

WHAT IS CLAIMED IS:

- 1 1. A method for treating cancer comprising administering to a subject
2 in need of such treatment a therapeutically effective amount of
3 (a) a member selected from an inhibitor of inosine monophosphate
4 dehydrogenase (IMPDH), an enantiomer of such a compound, a prodrug of such a
5 compound, a pharmaceutically acceptable salt of such a compound, and combinations
6 thereof; and
7 (b) an agent that inhibits a cellular process regulated by GTP or ATP.
- 1 2. The method of claim 1, wherein the agent that inhibits a cellular
2 process regulated by GTP is selected from the group consisting of an inhibitor of α -
3 tubulin polymerization, a prodrug therefor, a pharmaceutically acceptable salt thereof,
4 and combinations thereof.
- 1 3. The method of claim 2, wherein the IMPDH inhibitor is selected
2 from the group consisting of mizoribine, mizoribine aglycone, mycophenolate mofetil,
3 tiazofurin, viramidine, and ribivarin.
- 1 4. The method of claim 2, wherein the α -tubulin polymerization
2 inhibitor is selected from the group consisting of indanocine, indanrorine, vincristine,
3 vinblastine, vinorelbine, combretastatin-A, and colchicine.
- 1 5. The method of claim 2, wherein the IMPDH inhibitor is mizoribine
2 and the α -tubulin polymerization inhibitor is indanocine.
- 1 6. The method of claim 2, wherein the cancer is a slow growing
2 cancer.
- 1 7. The method of claim 6, wherein the slow growing cancer has a
2 high rate of α -tubulin turnover.
- 1 8. The method of claim 6, wherein the slow growing cancer is
2 selected from the group consisting of chronic lymphocytic leukemia, chronic
3 myelogenous leukemia, non-Hodgkins lymphoma, multiple myeloma, chronic

4 granulocytic leukemia, cutaneous T cell lymphoma, low grade lymphomas, slow growing
5 breast cancer, slow growing prostate cancer, and slow growing thyroid cancer.

1 9. A composition for treating cancer in a subject in need of such
2 treatment comprising therapeutically effective amounts of

3 (a) a member selected from an inhibitor of inosine monophosphate
4 dehydrogenase (IMPDH), an enantiomer of such a compound, a prodrug of such a
5 compound, a pharmaceutically acceptable salt of such a compound, and combinations
6 thereof; and

7 (b) an agent that inhibits a cellular process regulated by GTP or ATP.

1 10. The composition of claim 9, wherein the agent that inhibits a
2 cellular process regulated by GTP is a member selected from an inhibitor of α -tubulin
3 polymerization, a prodrug therefor, or a pharmaceutically acceptable salt thereof, and
4 combinations thereof.

1 11. The composition of claim 10, wherein the IMPDH inhibitor is
2 selected from the group consisting of mizoribine, mizoribine aglycone, mycophenolate
3 mofetil, tiazofurin, viramidine, and ribivarin.

1 12. The composition of claim 10, wherein the α -tubulin polymerization
2 inhibitor is selected from the group consisting of indanocine, vincristine, vinblastine,
3 vinorelbine, combretastatin-A, and colchicine.

1 13. The composition of claim 10, wherein the IMPDH inhibitor is
2 mizoribine and the α -tubulin polymerization inhibitor is indanocine.

1 14. The method of claim 1, wherein the agent that inhibits a cellular
2 process regulated by GTP is a member selected from a precursor of 9-beta-D-
3 arabinofuranosylguanine 5'-triphosphate (Ara-GTP), a prodrug therefore, a
4 pharmaceutically acceptable salt thereof, and combinations thereof.

1 15. The method of claim 14, wherein the IMPDH inhibitor is selected
2 from the group consisting of mizoribine, mizoribine aglycone, mycophenolate mofetil,
3 tiazofurin, viramidine, and ribivarin.

- 1 16. The method of claim 14, wherein the precursor of Ara-GTP is
2 selected from the group consisting of guanine arabinoside (Ara-G) and Nelarabine.
- 1 17. The method of claim 14, wherein the cancer is a lymphoma or a
2 leukemia.
- 1 18. The composition of claim 9, wherein the agent that inhibits a
2 cellular process regulated by GTP is a member selected from a precursor of Ara-GTP, a
3 prodrug therefor, or a pharmaceutically acceptable salt thereof, and combinations thereof.
- 1 19. The composition of claim 18, wherein the IMPDH inhibitor is
2 selected from the group consisting of mizoribine, mizoribine aglycone, mycophenolate
3 mofetil, tiazofurin, viramidine, and ribivarin.
- 1 20. The composition of claim 18, wherein the precursor of Ara-GTP is
2 selected from the group consisting of guanine arabinoside (Ara-G) and Nelarabine.
- 1 21. The method of claim 1, wherein the agent that inhibits a cellular
2 process regulated by GTP is a member selected from an inhibitor of the *de novo* pathway
3 of purine biosynthesis, a prodrug therefor, or a pharmaceutically acceptable salt thereof,
4 and combinations thereof.
- 1 22. The method of claim 21, wherein the IMPDH inhibitor is selected
2 from the group consisting of mizoribine, mizoribine aglycone, mycophenolate mofetil,
3 tiazofurin, viramidine, and ribivarin.
- 1 23. The method of claim 21, wherein the IMPDH inhibitor is
2 mizoribine.
- 1 24. The method of claim 21, wherein the IMPDH inhibitor is
2 mizoribine aglycone.
- 1 25. The method of claim 21, wherein the inhibitor of the *de novo*
2 pathway of purine biosynthesis is selected from the group consisting of L-alanosine,
3 methotrexate, trimetrexate, 10-propargyl-5,8-dideazafolic acid (PDDF), *N*-[5-[*N*-(3,4-
4 dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-*N*-methylamino]-2-thenoyl]-L-glutamic
5 acid (ZD1694, Tomudex), *N*-[4-[2-(2-amino-3,4-dihydro-4-oxo-7*H*-pyrrolo[2,3-*d*]-

6 pyrimidin-5-yl)ethyl]-benzoyl]-L-glutamic acid (LY231514), 6-(2'-formyl-2'naphthyl-
7 ethyl)-2-amino-4(3*H*)-oxoquinazoline (LL95509), (6*R,S*)-5,10-dideazatetrahydrofolic
8 acid (DDATHF), 4-[2-(2-amino-4-oxo-4,6,7,8-tetrahydro-3*H*pyrimidino[5,4,6][1,4]-
9 thiazin-6yl)-(S)-ethyl]-2,5-thienoylamino-L-glutamic acid (AG2034), and *N*-[5-(2-[(2,6-
10 diamino-4(3*H*)-oxopyrimidin-5-yl)thio]ethyl)thieno-2-yl]-L-glutamic acid (AG2009).

1 26. The method of claim 21, wherein the cancer comprises a
2 population of cells deficient in the enzyme methyladenosine phosphorylase (MTAP).

1 27. A method for treating cancer in a subject in need of such treatment,
2 wherein the cancer comprises of a population of cells deficient in the enzyme
3 methyladenosine phosphorylase (MTAP), comprising:

4 administering to the subject a therapeutically effective amount of a
5 member selected from an inhibitor of inosine monophosphate dehydrogenase (IMPDH),
6 an enantiomer of such a compound, a prodrug of such a compound, a pharmaceutically
7 acceptable salt of such a compound, and combinations thereof.

1 28. The method of claim 27, wherein the IMPDH inhibitor is selected
2 from the group consisting of mizoribine, mizoribine aglycone, mycophenolate mofetil,
3 tiazofurin, viramidine, and ribivarin.

1 29. The method of claim 27, wherein the IMPDH inhibitor is
2 mizoribine.

1 30. The method of claim 27, wherein the IMPDH inhibitor is
2 mizoribine aglycone.

1 31. The composition of claim 9, wherein the agent that inhibits a
2 cellular process regulated by GTP is a member selected from an inhibitor of the de novo
3 pathway of purine biosynthesis, a prodrug therefor, a pharmaceutically acceptable salt
4 thereof, and combinations thereof.

1 32. The composition of claim 31, wherein the IMPDH inhibitor is
2 selected from the group consisting of mizoribine, mizoribine aglycone, mycophenolate
3 mofetil, tiazofurin, viramidine, and ribivarin.

1 33. The composition of claim 31, wherein the inhibitor of the de novo
2 pathway of purine biosynthesis is selected from the group consisting of L-alanosine,
3 methotrexate, trimetrexate, 10-propargyl-5,8-dideazafolic acid (PDDF), *N*-[5-[*N*-(3,4-
4 dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-*N*-methylamino]-2-thenoyl]-L-glutamic
5 acid (ZD1694, Tomudex), *N*-[4-[2-(2-amino-3,4-dihydro-4-oxo-7*H*-pyrrolo[2,3-*d*]-
6 pyrimidin-5-yl)ethyl]-benzoyl]-L-glutamic acid (LY231514), 6-(2'-formyl-2'naphthyl-
7 ethyl)-2-amino-4(3*H*)-oxoquinazoline (LL95509), (6*R,S*)-5,10-dideazatetrahydrofolic
8 acid (DDATHF), 4-[2-(2-amino-4-oxo-4,6,7,8-tetrahydro-3*H*pyrimidino[5,4,6][1,4]-
9 thiazin-6yl)-(S)-ethyl]-2,5-thienoylamino-L-glutamic acid (AG2034), and *N*-[5-(2-[(2,6-
10 diamino-4(3*H*)-oxopyrimidin-5-yl)thio]ethyl)thieno-2-yl]-L-glutamic acid (AG2009).

1 34. The composition of claim 31, wherein the inhibitor of the de novo
2 pathway of purine biosynthesis is L-alanosine.

1 35. The method of claim 1, wherein the agent that inhibits a cellular
2 process regulated by GTP is an antagonist of a G-protein coupled receptor (GPCR).

1 36. The method of claim 35, wherein the IMPDH inhibitor is selected
2 from the group consisting of mizoribine, mizoribine aglycone, mycophenolate mofetil,
3 tiazofurin, viramidine, and ribivarin.

1 37. The method of claim 35, wherein the GPCR antagonist is selected
2 from the group consisting of atrasentan, leuprolide, goserelin, and octreotide.

1 38. The method of claim 35, wherein the cancer is prostate cancer.

1 39. The composition of claim 9, wherein the agent that inhibits a
2 cellular process regulated by GTP is a member selected from an antagonist of a G-protein
3 coupled receptor (GPCR), a prodrug therefor, or a pharmaceutically acceptable salt
4 thereof.

1 40. The composition of claim 39, wherein the IMPDH inhibitor is
2 selected from the group consisting of mizoribine, mizoribine aglycone, mycophenolate
3 mofetil, tiazofurin, viramidine, and ribivarin.

1 41. The composition of claim 39, wherein the GPCR antagonist is
2 selected from the group consisting of atrasentan, leuprolide, goserelin, and octreotide.

42. A compound having the formula:



wherein

R¹ is a member selected from H, substituted or unsubstituted alkyl,
substituted or unsubstituted heteroalkyl and saccharyl moieties;

X is a member selected from O, S and NR²

in which

R² is a member selected from H, substituted or unsubstituted alkyl,
substituted or unsubstituted heteroalkyl, OH and NH₂;

Y is a member selected from OR³ and NHR³

in which

R³ is a member selected from H, substituted or unsubstituted alkyl,
substituted or unsubstituted heteroalkyl, acyl and
P(O)OR¹²R¹³

wherein

R¹² and R¹³ are members independently selected from H,
substituted or unsubstituted alkyl, substituted or
unsubstituted heteroalkyl, acyl, acyloxyalkyl, and a
single bond to an oxygen of said saccharyl of R¹;

Z is a member selected from NR⁴R⁵, OR⁴ and SR⁴

in which

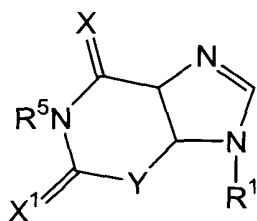
R⁴ is a member selected from H, substituted or unsubstituted alkyl,
substituted or unsubstituted heteroalkyl, a single bond to R³
and acyl;

R⁵ is a member selected from H, substituted or unsubstituted alkyl,
substituted or unsubstituted heteroalkyl, acyl,

acyloxycarbonyl, amino acid, peptidyl and acyloxyalkyl moieties; and

R^3 and R^4 , together with the atoms to which they are attached, are optionally joined to form a 6-membered heterocyclic ring; when R^3 is $P(O)OR^{12}R^{13}$, and R^1 is a saccharyl moiety, R^{13} and said saccharyl moiety and the atoms to which they are attached are optionally joined to form an 8-membered heterocyclic ring, with the proviso that said compound includes at least one of said 6-membered or said 8-membered heterocyclic ring system.

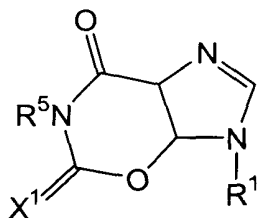
43. The compound according to claim 42, having the formula:



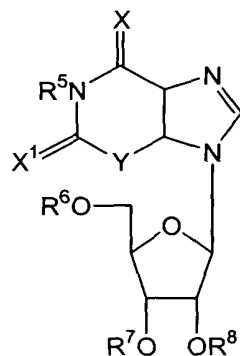
in which

X^1 is a member selected from O and S.

44. The compound according to claim 43, having the formula:



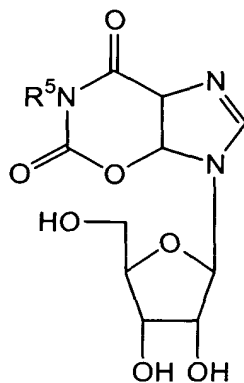
45. The compound according to claim 43 having the formula:



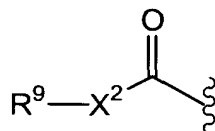
wherein

R^6 , R^7 and R^8 are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl and acyl moieties.

46. The compound according to claim 45 having the formula:



47. The compound according to claim 42, wherein R^5 has the formula:



wherein

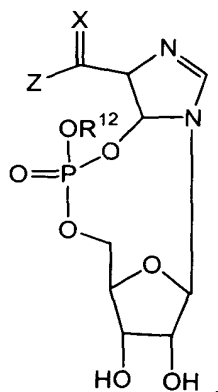
X^2 is a member selected from O, $CHR^{10}R^{11}$, and $OC(O)$

wherein

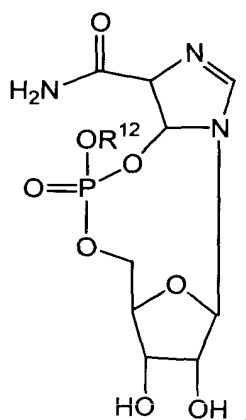
R^{10} and R^{11} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, NH_2 , NH_3^+ , $COOH$, COO^- , OH , and SH ; and

R^9 is a member selected from H, substituted or unsubstituted alkyl, and substituted or unsubstituted heteroalkyl.

48. The compound according to claim 42 having the formula:



49. The compound according to claim 48, having the formula:



1 50. A pharmaceutical formulation comprising a compound according
2 to claim 42 and a pharmaceutically acceptable carrier.

1 51. A method for treating cancer comprising administering to a subject
2 in need of such treatment a compound selected from the group consisting of mizoribine,
3 mizoribine aglycone, prodrugs of mizoribine, and prodrugs of mizoribine aglycone ,
4 wherein the compound is administered in an amount sufficient to maintain a plasma level
5 of the compound of between 0.5 and 50 micromolar for between 6 and 72 hours.

1 52. The method of claim 51, wherein the plasma level of compound is
2 between 1 and 30 micromolar for between 8 and 48 hours.

1 53. The method of claim 51, wherein the plasma level of compound is
2 between 5 and 25 micromolar for between 10 and 24 hours.

1 54. The method of claim 51, wherein the plasma level of compound is
2 at least 10 micromolar for at least 12 hours.

1 55. The method of claim 51, wherein the compound comprises a
2 pharmaceutically acceptable carrier.

1 56. The method of claim 51, wherein the compound is administered
2 parenterally.

1 57. The method of claim 51, wherein the compound is administered
2 orally.

1 58. The method of claim 51, wherein the compound is described by the
2 formula of claim 42.

1 59. A method of treating an immune system condition by providing an
2 immunosuppressive agent, the method comprising administering to a subject in need of
3 such treatment a therapeutically effective amount of a compound described by the
4 formula of claim 42.

1 60. The method of claim 59, wherein the compound comprises a
2 pharmaceutical carrier.

1 61. The method of claim 59, wherein the immune system condition is
2 rejection of a transplanted organ.

1 62. The method of claim 59, wherein the immune system condition is
2 an autoimmune disease.